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REMARKS

Claims 1-11 are pending in the application. Reconsideration is requested.

Claims 1, 3 and 5 have been amended to recite that the *P. falciparum* MSP-1_{42} is recombinantly expressed in *E. coli* as a soluble protein that retains its native structure. This amendment is supported in the specification, for example, in the paragraph beginning at page 11, line 31, and at page 13, lines 22-24. Claims 1 and 3 have also been amended to correct minor informalities. No new matter has been added.

The disclosure was objected to for lack of complete information. The specification will be amended to include the ATCC depository information as soon as it is received by the undersigned.

Rejection Under 35 U.S.C. § 112, first paragraph

Claims 1-11 were rejected under 35 U.S.C. §112, first paragraph, as failing to provide an enabling disclosure without complete evidence that the claimed biological materials are known and readily available to the public or complete evidence of the deposit of biological materials. This rejection is respectfully traversed. It is respectfully submitted that none of claims 1-11 requires the use of a particular construct, and that given the teachings of the specification, persons of skill in the art would be able to make and use the invention without reliance on a particular biological deposit.

The specification will be amended to insert the required information on the ATCC Deposit as soon as it is received by the undersigned.

Claim objections

Claim 3 was objected to because the abbreviation MSP-1_{42} was used without definition in its first occurrence. Claim 3 has been amended to insert the full name of the protein fragment. Claim 1 has been similarly amended, as the first occurrence of the abbreviation occurs in Claim

1.

In item 8 of the Action, Claims 3 and 5 appear to be objected to because of the terminology used. However, the Examiner's position is not clear. Further clarification is requested. The Examiner's suggestions on how to overcome the objection would be welcome.

Rejections under 35 U.S.C. § 103

Claims 1-11 were rejected under 35 U.S.C. §103 as being unpatentable over Kumar et al. or Chang et al. in view of Genton et al.. According to the Examiner's position, Kumar teaches a vaccine composition comprising recombinant *P. falciparum* MSP-1_{42}, FVO strain and Freund's adjuvant and a method of inducing an immune response to recombinant MSP-1_{42} in Aotus monkeys by injecting recombinant protein in Freund's adjuvant. The Examiner further states that Chang et al. teach a vaccine composition comprising a recombinant baculovirus 42 KD protein, i.e. MSP-1_{42} from *P. falciparum*, FUP strain and complete Freund's adjuvant. The Examiner also states that in both cases, sera from immunized monkeys were incubated with parasites to show production of effective protection.

It is the Examiner's position that it would be obvious to a person of skill in the art to combine either Kumar or Chang with Genton et al., who teach the use of adjuvant B in a blood stage malaria vaccine that includes MSP 1 and MSP 2 from *P. falciparum* 3D7 to obtain the present invention. This rejection is traversed for the following reasons.

The present invention is a malaria vaccine comprising *P. falciparum* MSP-1_{42} derived from *E. coli* and expressed as a soluble protein such that it retains its native folding. In a particularly preferred embodiment, the antigen is derived from the 3D7 strain of *P. falciparum*. An important feature of the present invention is the expression of the antigen in a native functional form that is capable of inducing a substantial level of protective immunity.

Kumar et al. evaluated two different antigens, an *E. coli* GST-MSP-1_{42} fusion protein and a 19 kD yeast-expressed fragment, which causes some confusion for interpreting the results. These antigens are both derived from the FVO strain of *P. falciparum*. The MSP-1_{42} portion of the GST-MSP-1_{42} fusion protein is the one that is most similar to the presently used protein from

the 3D7 strain but is about 50% different in primary structure especially in the N-terminal two thirds of the molecule. In addition, the GST-MSP-1_{42} fusion protein of Kumar contains approximately 200 additional amino acids that come from GST, and increases the molecular weight by about 25 kD. The substantial difference in the two proteins leads to different outcomes in purification strategy, and in the resulting functionality of the product as a vaccine. The *E. coli* fusion protein of Kumar was not purified in a way that would lead to a protein that was properly stabilized by disulfide bridges, as in the present invention. Kumar et al. discloses a composition that includes a GSP fusion with an antigen from MSP-42 that is purified and eluted with reduced glutathione. No further description of the purification is provided, and in particular, nothing that would lead to the required disulfide bridges that are necessary for the functionality of the present invention. The antibody titers reported by Kumar et al. in response to their disclosed vaccine are substantially lower than the levels that are achieved by the present invention using a regimen that contains a lower amount of active substance. This can be seen by comparing the values in Table 1 of Kumar et al. with the values reported in of the present specification in Table 6 at page 69. Because of the form in which the data is presented, this comparison can be made only indirectly owing to differences in the species vaccinated (Kumar, Aotus monkeys; present invention, humans), dose (Kumar 200 μg/dose; present invention 50 μg/dose) and adjuvant (Kumar, Freund's Adjuvant, which is the most potent immunological adjuvant known; present invention, ASO2A, which is an adjuvant that is useful for human application and is significantly less potent than Fruend's). Despite these differences the current invention induced at least 5 times higher ELISA reactive $MSP1_{42}$ –specific antibodies than did the GST-MSP-1_{42} fusion protein from Kumar. Our direct comparisons show that Aotus monkeys vaccinated with the present invention in Freund's adjuvant produced about 300 times more antibodies that those vaccinated with the present invention in AS02A. Thus the inherent immunogenicity of the current invention is about 1000 times greater than the GST-MSP-1_{42} fusion protein of Kumar.

Finally, it is particularly noted that after comparing the GST-MSP-1_{42} fusion protein and the $MSP1_{19}$ protein vaccines, Kumar rejected the GST-MSP-1_{42} fusion protein as a vaccine that

lacked potency in favor of the $MSP1_{19}$ protein vaccine.

Thus, the presently claimed vaccine differs from Kumar et al. in at least the following ways:

1. The primary structure of FVO (Kumar) is approximately 50% different from the primary structure of 3D7 (the present invention);

2. The protein of Kumar is not expressed as a recombinant soluble protein from *E. coli* that retains its native structure.

3. The protein of Kumar is not purified in a way that would lead to proper stabilization by disulfide bridges; and

4. The antibody titers reported by Kumar et al. are much lower than those achieved with the presently claimed vaccine.

The Examiner has relied upon Genton et al. for teaching the use of Adjuvant B in a malaria vaccine (see page 8, first full paragraph, of the Office Action). However, Genton et al. does not remedy the deficiency of Kumar et al. to disclose a vaccine comprising an $MSP\text{-}1_{42}$ protein that is expressed as a soluble protein from *E. coli*. It is respectfully submitted that if Genton et al. had been combined with Kumar as proposed by the Examiner, it would have resulted a vaccine that comprised the fusion protein as taught by Kumar et al., and not the $MSP\text{-}1_{42}$ protein that is expressed as a soluble protein from *E. coli* that retains its native structure of the presently claimed vaccine. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

Chang et al. discloses a baculovirus recombinant polypeptide based on *P. falciparum* MSP-1 derived from the FUP isolate, and isolated by affinity chromatography. It is respectfully submitted that Chang et al., like Kumar et al., does not teach or suggest a vaccine comprising *P. falciparum* $MSP\text{-}1_{42}$ that is expressed in *E. coli* as a soluble protein. For the reasons presented above, Genton et al. does not remedy this deficiency. The combination of Chang et al. with Genton et al. will result in a vaccine comprising a baculovirus recombinant peptide as taught by Chang et al., and not the $MSP\text{-}1_{42}$ protein that is expressed as a soluble protein from *E. coli* that retains its native structure of the presently claimed vaccine. Accordingly, reconsideration and

withdrawal of the rejection are respectfully requested.

All objections and rejections having been addressed, it is respectfully requested that the rejections be withdrawn and a Notice of Allowance issued. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is hereby invited to telephone the undersigned at the number provided.

Respectfully submitted,

Ann S. Hobbs, Ph.D.
Registration No. 36,830
Venable
P.O. Box 34385
Washington, D.C. 20043-9998
Telephone: (202) 344-4651
Telefax: (202) 344-8300